



## RESEARCH ARTICLE

## Doppler Echocardiography Evaluation of the Relationship between Insulin Resistance and Early Diastolic Dysfunction in Prediabetes Patients

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### Abstract

Diabetes mellitus (DM) is known to be associated with serious cardiovascular risk and the prevalence of DM amongst population is rapidly increasing. When important risk factors such as age, hypercholesterolemia, obesity and coronary artery disease are excluded, DM still continues to be an important risk factor for cardiovascular disease. Diastolic dysfunction is an early complication of type 2 diabetes and diabetic cardiomyopathy is known to be the first step of the process. Diabetic cardiomyopathy is progressive, it leads to a decrease in systolic and diastolic functions; and, without clinical signs, and diastolic dysfunction can be detected by echocardiography where tissue Doppler studies and left atrial volume measurements could be performed. As prediabetes holds a potential risk for development of type 2 diabetes; in the same way, it possesses microvascular and cardiovascular risk factors. The association of type 2 diabetes with left ventricular function and diastolic dysfunction has been explored in many studies. But, studies on relationship of prediabetes, subgroups of prediabetes and insulin resistance with left ventricular function are limited; therefore, investigation of diastolic function in patients with prediabetes was aimed in this study. Prediabetic patients with normal hypertension, between the ages of 18-50, who do not have any other systemic disease, were included in the study and echocardiography investigation was carried out on all patients. Diastolic dysfunction was detected in 10 patients. Diastolic dysfunction and HOMA-IR levels ( $p = 0.002$ ), triglyceride levels ( $p = 0.003$ ) and the presence of insulin resistance ( $p = 0.001$ ) demonstrated a statistically significant correlation with diastolic dysfunction. However impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) revealed no statistically significant correlation with the presence of diastolic dysfunction.

Diastolic dysfunction is one of the major concerns in cardiovascular disease; and, can be detected with standard Doppler echocardiography investigation in prediabetes patients. Changes associated with diastolic dysfunction demonstrated a particularly strong relationship with higher HOMA-IR levels. Especially in patients with pre-diabetes or insulin resistance, importance of detailed echocardiography investigation should be emphasized. Early detection and primary prevention of cardiovascular disease could be enhanced with the use of echocardiography investigation.

### Keywords

Prediabetes, Insulin resistance, Diastolic dysfunction, HOMA-IR

### Introduction

Type 2 DM is characterized by peripheral insulin resistance, loss of islet beta cells and decrease in secretion of insulin hormone. DM is associated with risk of serious cardiovascular problems and the prevalence is increasing rapidly.

Even when other risk factors for cardiovascular disease such as age, hypercholesterolemia, obesity and coronary artery disease are excluded, DM still continues to possess an important risk. Diastolic dysfunction is an early complication of DM and it is believed to be the first step in diabetic cardiomyopathy. Diabetic cardiomyopathy is characterized by decrease in both systolic and diastolic function in absence of hypertension, coronary artery disease and left ventricular hypertrophy. Diabetic cardiomyopathy is pro-



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gressive and leads to a reduction in systolic and diastolic function; although this dysfunction does not give clinical signs, it can be detected by echocardiography [1].

Prediabetes is a state of potential risk for development of DM and in the same way, for development of microvascular and cardiovascular risk factors. Although many studies have been performed about DM and left ventricular dysfunction, studies associated with prediabetes, prediabetes subgroups and insulin resistance are insufficient.

Cardiac damage caused by DM can also possibly take place in the prediabetic period. In this study, our goal is to investigate presence of the cardiac damage in prediabetic period and enlighten the subject of preventative measures that could be taken at an early stage [2].

## Patients and Methods

GATA Haydarpasa Training Hospital Non-Interventional Studies Clinical Research Ethics Committee approval numbered 2012-129 has been obtained on the date of 11.29.2012.

50 prediabetic patients admitted to GATA Haydarpasa Training Hospital internal medicine outpatient clinic between November 2012 and May 2013, who are in 18-50 age group, with normal blood pressure, having impaired fasting glucose and/or impaired glucose tolerance with no coronary or structural heart disease history were included in this study. The aim of this study was to assess the diastolic function in prediabetic patients. Therefore, clinical conditions that could lead to diastolic dysfunction were excluded from the study. Informed consent was obtained from all patients who were included in the study. Exclusion criteria included history of myocardial infarction, coronary artery disease, regional wall motion abnormalities in resting echocardiography, evidence of ischemia in electrocardiography, valvular and structural heart disease, blood pressure higher than 140/90 mmHg or use of antihypertensive medications, chronic kidney disease, chronic obstructive lung disease, age over 50 and any other chronic diseases.

All patients were questioned in detail about the history of all cardiac diseases. Detailed physical examination, blood pressure measurement, waist circumference, biochemical tests and echocardiographic measurements were recorded. Body mass index was calculated by using the weight/height<sup>2</sup> (kg/m<sup>2</sup>) formula. Prediabetes diagnosis was made according to the ADA criteria. All biochemical examinations were carried out after 8 hours of fasting. Fasting plasma glucose value of 100-126 mg/dL was considered to be classified as impaired fasting glucose and two hours of 75 gr oral glucose tolerance test was performed on these patients. After this, patients with 2 hour plasma glucose value of 140-200 mg/dL considered to have impaired glucose tolerance. Patients with HbA1c value ranging 5.7 to 6.5% were considered to be prediabetic. Additionally, insulin levels, lipid profile, liver and kidney function,

electrolytes, thyroid function and presence of anemia were evaluated with biochemical blood tests. Presence of insulin resistance and test results were evaluated by using the HOMA-IR test. HOMA-IR was calculated by the following formula.

$$\text{HOMA-IR} = \text{fasting plasma insulin (U/ml)} \times \text{fasting glucose (mg/dl)} \times 0.0555/22.5$$

**Echocardiographic Evaluation:** Echocardiography was performed in all patients participating in the study. 2 dimensional color Doppler echocardiographic tests were performed with Philips-Matrix IE33 Doppler device. From apical 4<sup>th</sup> and 5<sup>th</sup> of the image space, transmitral flow patterns were obtained by using pulsed-wave (PW) Doppler. Additionally, diastolic parameters of left ventricle like early diastolic flow signal (E velocity, cm/sec), atrial contraction signal (the velocity, cm/sec), E/ ratio, deceleration time (DT; ms), iso volumetric relaxation time (IVRT; ms); and, apical two-chamber images from the respective end-diastolic volume (EDV; mL), end-systolic volume (ESV; mL), stroke volume (SV; mL) and left ventricular ejection fraction (LVEF; %) were calculated as the systolic parameters. Echocardiography tests were performed and interpreted by the same cardiologist.

## Statistical Analysis

SPSS 18.0 software was used for statistical analysis. Descriptive analysis of frequency tables for categorical variables, percentiles for descriptive analysis of continuous variables, measures of central tendency and dispersion characteristics of the data were used in the analysis of our study. For the comparison of data, Chi-square test was used. Comparison of continuous independent and binomial categorical dependent variables done by univariate logistic regression test. Analysis of single regression to find the statistical significance amongst for two continuous variables, was performed with multi collinearity analysis. As a result of Spearman correlation analysis, we found  $P < 0.5$  and  $r > 0.60$  so multivariate logistic regression was not applied.

## Results

50 patients participated in the study, of which 26 were male (52%) and 24 were female (48%). The average age of patients was 44.20. The mean BMI of the patients was 29.36 kg/m<sup>2</sup>, with the highest BMI being 42 kg/m<sup>2</sup> and the lowest BMI being 22 kg/m<sup>2</sup>. The average abdominal circumference was found to be 95 cm, the highest abdominal circumference was 130 cm and the minimum abdominal circumference was 80 cm. The average fasting blood glucose of the patients was 107 mg/dL, the mean fasting plasma insulin level was 22.75; and, HOMA-IR levels were determined as an average of 3.5. In biochemical test results, the average LDL cholesterol value was  $120 \pm 35.57$  mg/dL, the mean triglyceride level was  $130.5 \pm 69.39$  mg/dL, the mean HDL cholesterol level was  $51.5 \pm 1.75$ , the mean HbA1c value was  $6 \pm 0.42$  and 2-hour OGTT average was  $153 \pm 31.43$ . 46

**Table 1:** Insulin resistance and diastolic dysfunction relationship.

		Diastolic dysfunction		
		Yes	No	Total
Insulin resistance	Yes	10 (35.7%)	18 (64.3%)	28
	No	0 (0.0%)	22 (100.0%)	22
	Total	10 (20.0%)	40 (80.0%)	50
Fisher exact test		P = 0.01		

**Table 2:** Logistic regression analysis (\* = statistically significant).

Parameters	P value	Relative risk
Age and diastolic dysfunction	0.409	0.952
BMI and diastolic dysfunction	0.380	1.081
Waist circumference and diastolic dysfunction	0.645	1.015
Fasting blood glucose and diastolic dysfunction	0.326	0.962
Homa-IR level and diastolic dysfunction	0.002*	2.492
Insulin level and diastolic dysfunction	0.000	0.113
LDL levels and diastolic dysfunction	0.288	1.011
HDL levels and diastolic dysfunction	0.168	0.952
Triglyceride levels and diastolic dysfunction	0.003	1.017
HbA1C levels and diastolic dysfunction	0.815	1.218
OGTT results and diastolic dysfunction	0.777	1.003

(92%) prediabetic patients had impaired fasting glucose, 34 (68%) had impaired glucose tolerance, 32 (64%) patients had both impaired fasting glucose and impaired glucose tolerance. HOMA-IR  $\geq 2.6$  was considered to possess insulin resistance and in 28 patients (56%), insulin resistance was identified. Standard echocardiography was performed on normotensive patients who had no additional diseases demonstrated by medical history, physical examination and biochemical tests, other than prediabetes. Primary valve disease, systolic function, wall thickness and structural heart disease parameters were evaluated. These patients were also examined by Doppler echocardiography in order to assess their diastolic functions. Echocardiographic examinations were performed in 50 patients and diastolic dysfunction was detected in 10 (20%) of the patients. Patients with E/A ratio below 1 were accepted to have stage 1 diastolic dysfunction. The results of the relationship between insulin resistance and diastolic dysfunction are demonstrated in [Table 1](#).

Gender, fasting blood sugar values, insulin levels, HOMA-IR, the presence of insulin resistance, IFG, IGT, LDL cholesterol, HDL cholesterol, and triglyceride levels were studied in relation to diastolic dysfunction. Chi-square test was applied for analysis of the relationship between gender and diastolic dysfunction. 3 (11.5%) male and 7 (29.2%) female patients were identified to have diastolic dysfunction. No statistically significant relationship was established between sex and diastolic dysfunction ( $p = 0.229$ ). There was no statistically significant association

between IFG and diastolic dysfunction ( $p = 0.164$ ), between BGT and diastolic dysfunction ( $p = 0.600$ ); and, between diastolic dysfunction and patients who had both IGT and IFG ( $p = 0.730$ ). Statistically significant relationship was found between presence of insulin resistance (HOMA-IR  $\geq 2.6$ ) and diastolic dysfunction ( $p = 0.001$ ). Age, BMI, waist circumference, fasting blood glucose, HOMA-IR, insulin, LDL cholesterol, HDL cholesterol, triglycerides, HbA1c levels and relationship with diastolic dysfunction were evaluated by logistic regression analysis. Statistically significant relationship was found between diastolic dysfunction and both HOMA-IR levels ( $p = 0.002$ ) and triglyceride levels ( $p = 0.003$ ); but, other parameters were found not to have a statistically significant relationship with diastolic dysfunction. Results of the logistic regression analysis are demonstrated in [Table 2](#).

## Discussion

Deaths from diabetes are 65% due to cardiovascular risk factors. Risk is increased 2-4 fold for coronary artery disease, 2-5 folds for stroke and 2-4 fold for type 2 diabetes mellitus. In Euro Heart Survey study, out of all patients who developed cardiovascular disease, one in every two patients had impaired fasting glucose, impaired glucose tolerance, or both. In the Nurses Health Study, after cardiovascular risk factors were assessed, patients with prediabetes developed more cardiovascular diseases compared to other individuals [3]. In a meta-analysis of 18 studies, patients with mean glycemic values above 100 mg/dL had 18% increased cardiovascular disease risk, patients with mean glycemic values above 110 mg/dL had 20% increased cardiovascular disease risk and patients who had impaired glucose tolerance had 20% increased cardiovascular disease risk. So, it was established that cardiovascular disease risk increased in prediabetic patients. A meta-analysis of 10 randomized trials that have been done with 23,152 patients showed us, lifestyle changes and the use of drugs in prediabetic patients decreased the development of diabetes up to the level of 30%, but led to no reduction in cardiovascular risk [4]. According to current research, cardiovascular risk reduction has not been achieved with glycemic control. This suggests that preventing mortality and morbidity related to cardiovascular disease in diabetes requires different approaches. In numerous studies, it has been shown that diastolic dysfunction is the first finding of myocardial disease in diabetes. This can be considered as the earliest preclinical finding of the diabetic cardiomyopathy [5,6]. Development of myocardial dysfunction in diabetes is a multifactorial process. Metabolic imbalance, changes in the extracellular matrix components, small vessel disease, insulin resistance and autonomic dysfunction could be listed as some of these factors. There is a significant need to improve the studies about cardio metabolic effects of hyperglycemia. In ADVANCE and ACCORD studies, it has been shown that intensive control of HbA1c is not useful in prevention of adverse cardiovascular outcomes.

The significance of cardiac involvement in the prediabetic period has not been clearly understood. Therefore, this study aimed to investigate the relationship between insulin resistance and presence of ventricular dysfunction in prediabetic patients.

This study has concluded that left ventricular diastolic dysfunction is associated with insulin resistance and this relationship is independent of ventricle structure, impaired glucose tolerance, obesity and lipid profile. E/A ratio provided useful results on determination of the diastolic dysfunction. Increase in the "A wave" and lengthening of the IVRT in patients who had diastolic dysfunction was remarkable. This demonstrates that, with increase in insulin resistance, progression of the left ventricle disorder could develop. The results which support these findings could be encountered in two similar studies in patients with prediabetes [7]. Moreover, studies that have been done with patients who have diabetes, obesity and metabolic syndrome provided similar findings; and, insulin resistance in three of the groups seemed to be the main cause [8-10]. The relationship between insulin resistance and myocardial performance has not been highlighted and explained adequately. However, the decrease in endothelium-dependent vasodilation and stimulation of vascular smooth muscle proliferation has been presented.

In a study on prediabetic patients, no statistically significant relationship was established between fasting plasma glucose or HbA1c levels and left ventricular dysfunction; but, a more important result, a significant relationship with diastolic dysfunction and insulin resistance was found [11,12]. In previous studies, researchers described a relationship between left ventricular dysfunction and visceral obesity; this relationship was also supported in the study of Wilfried and his colleagues [13]. There was also no relationship established between BMI and left ventricular function. In this study, no statistically significant correlation was found between left ventricular function and both waist circumference or BMI. Slim and Nasr described a relationship between visceral obesity and insulin resistance with left ventricular dysfunction but, the relationship between insulin resistance and diastolic dysfunction was found to be more significant. Visceral obesity and diastolic dysfunction relationship has also been found to be associated with insulin resistance that already exist in patients [8]. Especially in central obesity, release of inflammatory cytokines and proteins is highly probable. These inflammatory cytokines and proteins induce an effect on cardiac outcome and could result in stress-related hyperglycemia in prediabetic patients [14]. Also adipocytes, especially abdominal visceral adipocytes, release peptides that affect the vascular structure and functioning [15,16]. It is principally known that high blood pressure affects myocardial function, especially the diastolic function [17-19]. Because of that, high blood pressure was accepted as an exclusion criterion and only normotensive patients have been included in this study. When examining the relationship be-

tween lipid profile and diastolic dysfunction, a significant relationship between diastolic dysfunction and triglyceride levels have been only identified. This provided a result that is consistent with the study of Lisa and colleagues who stated that there is an independent relationship between triglyceride levels and E/A ratio [20].

Restrictive aspects of this study were availability of a small patient group, lack of a healthy control group, exclusion criteria of ischemic heart disease being limited to physical examination, medical history, and ECG tests; and, coronary imaging not being available. In this study, only standard techniques of Doppler echocardiography were used when evaluating diastolic functions as the aim was to demonstrate diastolic dysfunction by application of standard techniques, specific tissue Doppler was not used; this may be a restrictive aspect of this study.

In this study, it was identified that diastolic dysfunction detected with Doppler echocardiography has a strong relation to high HOMA-IR values. Therefore, it could be advised that significance of detailed echocardiographic examination should be emphasized for patients with evident insulin resistance.

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